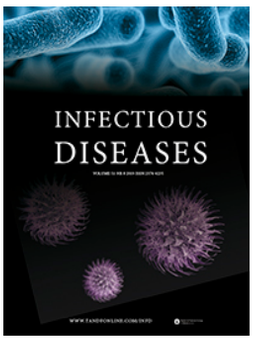

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Late onset sepsis in NICU – are we are all looking through the same lens?

Elsa da Palma Afonso & Stijn Blot

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LETTER TO THE EDITOR

Late onset sepsis in NICU – are we are all looking through the same lens?

To the Editor

We read with interest a study on demographic and clinical differences between late-onset sepsis caused by coagulase-negative staphylococci (CoNS) and other pathogens in a neonatal intensive care unit (NICU) [1] and found that relevant research questions and controversies still prevail in the subject of neonatal late-onset sepsis.

Neonatal sepsis is an infectious disease potentially complicating the course of the newborn infant and late-onset sepsis, which occurs after 72 h of extra-uterine life is a considerable cause of mortality and morbidity in newborns admitted to the NICU [2].

Epidemiological data from NICUs in the United Kingdom suggests most cases of late-onset sepsis, or healthcare-associated sepsis, are caused by gram-positive pathogens (70%); in preterm and very low-birthweight infants, gram-positive bacteria was responsible for 49% of all episodes of late-onset sepsis and the majority of those was coagulase-negative staphylococci [3]. In a large US study, CoNS was reported as the cause of nearly half of all cases of late-onset sepsis in preterm and very-low birthweight infants and, of all sepsis episodes caused by gram-positive pathogens, almost three-quarters was likely to be CoNS [4].

CoNS-related late-onset sepsis is more common but has a lower mortality rate when compared to sepsis caused by other pathogens. However, in susceptible infants, it is associated to significant morbidity, including poor long-term neurodevelopmental outcomes [5].

The article by Berlak et al. analyzed the demographic and clinical differences between neonates with late-onset sepsis caused by CoNS and other pathogens in a NICU in Israel [1].

Epidemiological trends in this retrospective study were consistent with the available literature: most identified cases of neonatal sepsis were caused by CoNS and mainly affected infants of lower gestational and chronological age. Patients with CoNS sepsis generally had non-significant variations in body temperature, lower rates of necrotizing enterocolitis, meningitis or neutropenia, and higher rates of parenteral nutrition than patients with sepsis caused by other pathogens [1].

In their multivariate analysis, the authors identified parenteral nutrition as the only independent risk factor for developing CoNS sepsis. Lipid infusions have previously been associated with increased rate of bloodstream infections in neonates [6]. Other known risk factors for late- onset sepsis are prolonged length of stay in the NICU, duration of central line use and mechanical ventilation, likely due to disruption of normal barrier functions and exposure to pathogenic microorganisms [4]. In fact, evidence shows that the increased risk for late-onset sepsis in infants on parenteral nutrition is associated with a delay in initiating/progressing enteral feeding [2]. However, this usually increases the risk for gram-negative pathogens, not particularly for CoNS.

It is noteworthy that Berlak et al. [1] found an association between CoNS-related sepsis and parenteral nutrition. However, even though there were slightly more sepsis episodes caused by CoNS in infants with central lines, this relationship was not statistically significant. On the other hand, an association – also not significant but thought-provoking – was found between non-CoNS sepsis and peripheral lines. Peripheral lines are often not even reported as risk factors and perhaps this could be worth looking into in future research, since the majority of infants admitted to NICU will have peripheral access and, as opposed to CVCs, insertion bundles are often not applied and handling practices are not streamlined. Moreover, it is unclear whether the use of peripheral cannulas increases the risk of sepsis in more vulnerable infants.

It is inevitable to highlight issues around the definition of sepsis used in this study. This is a controversial

subject and pointed out as a major factor affecting interpretation of studies [7].

The authors used the CDC definition of sepsis in adults, in which two blood cultures are drawn from two different intravenous sites and only if both were positive would they consider a sepsis with CoNS [8]. In paediatric and neonatal critical care patients, although a positive culture is often considered the 'gold standard' definition of infection, culture-negative, clinical sepsis is usually enough to warrant treatment. Likewise, a pathogen may be identified in as little as 36–51% of cases of sepsis in adults even though sepsis is defined as SIRS in response to an inciting infection - about half of sepsis episodes seen in pediatric patients are culture negative [7].

In neonates, a clinical scenario where blood cultures are negative, but the infant displays signs of clinical sepsis is far more common than blood-culture positive sepsis [9].

Furthermore, blood cultures with CoNS are among the most difficult microbiological findings to interpret. Contamination rates are considered high in the NICU and samples obtained from intravenous devices are prone to be contaminated with CoNS [10]. Positive blood cultures with great cluster growth and positive within 48 h of collection have been associated with an increased likelihood of significance, but are not unquestionably sensitive or specific, and may be affected by prior antibiotic use. This makes interpretation of results difficult and very dependent on clinical signs and symptoms associated to the suspected sepsis episode.

In a nutshell, the work of Berlak el al. [1] gives valuable insights into neonatal sepsis in a country- specific NICU setting, but also highlights the need for a consensual definition of neonatal sepsis and the true impact of not treating blood culture-negative late-onset sepsis.

Similarly, the real impact of parenteral nutrition and the role of central lines in neonatal sepsis should be clarified: where does the risk lie? Is it during insertion, is it the type of infusion or handling issues? Finally, some research could be dedicated to the neglected subject of peripheral lines and their role in late-onset sepsis in the NICU.

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Elsa da Palma Afonso
Neonatal Intensive Care Unit, Rosie Hospital, Cambridge University Hospitals NHS Trust, Cambridge, UK
Department of Internal Medicine, Faculty of Medicine & Health Science, Ghent University, Ghent, Belgium
elsa.Depalmaafonso@ugent.be

Stijn Blot
Department of Internal Medicine, Faculty of Medicine & Health Science, Ghent University, Ghent, Belgium
Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia

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